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Biliary Excretion and Tissue Distribution of Cadmium-109 Administered to Rats

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16. ABSTRACT

The difference in the excretion of cadmium in urine and feces was measured in rats with either ligated or intact bile ducts. Three days following a single oral-administration of cadmium-109 plus stable cadmium chloride, 4 x 10^{-3} percent of the dose was excreted in the urine of rats with intact bile ducts, while 5 x 10^{-2} percent was excreted in urine of rats with ligated bile ducts. While 82 percent of the dose was excreted via the feces of intact rats, 71 percent was recovered in feces from rats with ligated bile ducts. The amount of the dose recovered in tissue was 13 percent for intact rats and 30 percent for ligated rats.

Following intravenous administration of cadmium, rats with intact bile ducts excreted about 5 x 10^{-1} percent of the dose in urine versus 2 percent for rats with ligated bile ducts. About 8 percent of the dose was excreted via the feces of rats with intact bile ducts compared to only about 6 x 10^{-1} percent by ligated rats. The amount of the dose recovered in the tissues was 91 and 96 percent respectively for intact and ligated rats.

The liver appeared to be the primary organ of concern during the course of this study, although cadmium was also retained in the kidneys and bone.

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by

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FOREWORD

Protection of the environment requires effective regulatory actions based on sound technical and scientific data. The data must include the quantitative description and linking of pollutant sources, transport mechanisms, interactions, and resulting effects on man and his environment. Because of the complexities involved, assessment of exposure to specific pollutants in the environment requires a total systems approach that transcends the media of air, water, and land. The Environmental Monitoring Systems Laboratory at Las Vegas contributes to the formation and enhancement of a sound monitoring-data base for exposure assessment through programs designed to:

- develop and optimize systems and strategies for monitoring pollutants and their impact on the environment
- demonstrate new monitoring systems and technologies by applying them to fulfill special monitoring needs of the Agency's operating programs

This report presents the results of a study conducted to ascertain the role of bile in the excretion of cadmium following oral or intravenous administration of cadmium-109. The tissue distribution following the two routes of administration was also determined. This report is part of a series of investigations undertaken to establish the absorption/excretion characteristics of various metal pollutants in order to provide information for selection of relatively rapid mammalian tests for estimating exposure. This information will be useful for establishing baseline information prior to possible polluting events and for assessing environmental damage by measuring the exposure of biological monitors to the pollutants released. For further information the reader should contact the Exposure Assessment Division.

Glenn E. Schweitzer
Director
Environmental Monitoring Systems Laboratory
Las Vegas, Nevada

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INTRODUCTION

Cadmium is present as a trace metal in the earth's crust (1.8 to 5.5 x 10^{-5} percent) and as an impurity in ores of other metals such as lead, zinc, and nickel. The toxic effects of cadmium were brought to the world's attention in 1968 when the Japanese Ministry of Health and Welfare declared that itai-itai disease -- translated as "ouch-ouch" disease -- was the result of renal tubular impairment caused by cadmium poisoning (Tsuchiya 1976).

Cadmium is used in electroplating and in the manufacture of photographic pigments, paints, and plastics. It is emitted to the air as a waste product of metal refineries and is a contaminant of phosphate fertilizers and sewage sludge (Friberg et al. 1971; Athanassiadas 1971).

Human exposure to cadmium is through ingestion of food such as fish, rice, vegetables, sugar, and tea, or through smoking products containing contaminated tobacco (Friberg 1971, 1973; Underwood 1977).

Animals grazing on pastures fertilized with superphosphates or contaminated by industrial sources ingest cadmium in grasses and clovers, and in Japan, cadmium is found in rice straw taken from polluted paddy fields (Underwood 1977).

Summarizing the work of others, Underwood (1977) provides a good review of the information on cadmium metabolism and toxicity. His review considers the important point concerning cadmium metabolism to be the lack of an effective homeostatic control mechanism resulting in a gradual buildup of cadmium in the body with age caused by the long biological half-life of cadmium estimated to be 16 to 33 years in man and about 200 days in rats.

Complex interactions which occur between cadmium and other divalent cations: i.e. zinc, copper, iron, calcium and selenium, make predicting the dose very difficult. For instance, cadmium uptake by the cell mucosa of the rat intestine is enhanced by zinc at 10^{-5} or 10^{-3} molarity and depressed at higher zinc concentrations (Sahagian et al. 1967). Kobayashi et al. (1971) has presented evidence that cadmium lowers the absorption of calcium and increases its excretion from the digestive tract. Fox (1976) showed that supplementing the diet of Japanese quail with zinc, manganese and copper above the requirement level, decreased cadmium concentration in the liver and kidneys.

Cadmium has been shown to be the cause of hypertension in rats, rabbits and dogs. When administered in amounts less than those required to induce signs of toxicity, hypertension occurs, whereas at higher dose levels,

hypertension does not develop and systolic pressure in rats may actually decrease (Underwood 1977).

Systemic administration of cadmium salts can produce testicular necrosis in species possessing scrotal testes but not in those having abdominal testes. Testicular damage can be diminished by injections of zinc, estrogen, thio compounds, cysteine, selenium, cobalt or dimercaptopropanol (Neathery and Miller 1975). Although prepubertal and pregnant females are highly sensitive to cadmium, fertility or fecundity are not affected in the adult non-pregnant female. Egg production in laying hens is reduced by 50 ppm of dietary cadmium (Neathery and Miller 1975).

From the previous summary of the environmental impact of cadmium and the complexity of its biochemistry, it is obvious that a reliable monitoring system for cadmium is essential. This study was undertaken to provide further information on the excretion of cadmium by the rat in an effort to select universally available biological monitors, and to provide a reliable method for quickly (estimating) exposure of individuals (humans, etc.) to a potentially hazardous pollutant.

CONCLUSIONS AND RECOMMENDATIONS

This investigation has clearly demonstrated that bile plays an important role in the concentration and transport of cadmium for subsequent readsorption or excretion. Collection of bile from animals endemic to a potentially polluted area would enable an investigator to easily determine an early increase in biologically available cadmium. However, caution must be exercised when attempting to correlate the amount of cadmium in the bile with the dose of cadmium received, as dose threshold effects and possible synergistic reactions with other pollutants may affect the kinetics of bile production.

EXPERIMENTAL PROCEDURES

Two groups of 16 female Wistar rats, 85-day-old young adults, weighing 190 ± 40 grams, were used for this study. To determine the amount of cadmium excreted in the bile, the difference in excretion of cadmium in urine and feces was measured in rats with either ligated or intact bile ducts.

To facilitate the analysis of samples, cadmium-109 as the chloride was administered along with stable cadmium carrier. Prior to administration of the radionuclide, the common bile duct of six animals in each group was ligated. Food was withheld for 12 hours prior to surgery. The rats were anesthetized with Fluothane® and the bile duct ligated at a point 5 or 6 millimeters below the hilus at the liver and just above where the pancreatic tissue no longer surrounded it. A surgical procedure as described by Lambert (1970) was modified for use in this procedure. One hour after ligation of the bile duct, when the animal had recovered from the anesthetic, 5 μCi of cadmium-109 plus 25 mg of $CdCl_2$ per kilogram of body weight was administered orally by means of a dosing needle and syringe. Six more animals were treated in the same manner but without ligation of the bile duct. The 12 animals plus 4 controls were placed in stainless steel metabolism cages and maintained on commercial laboratory rat chow and deionized water. Total urine and feces samples were collected every 12 hours, weighed, and analyzed by gamma spectrometry. The following day the second group of 16 animals was treated in the same manner as the first group, but following ligation, the animals were administered 1 microcurie (μCi) of cadmium-109 plus 5 mg of stable cadmium chloride carrier per kilogram of body weight by intravenous injection into the tail vein. Samples were collected in the same manner as for the preceding group. Three days following administration of the radionuclide, the animals were weighed and sacrificed by anesthetic overdose. Blood was removed by cardiac puncture. Tissue samples were removed, weighed, and placed in scintillation vials containing formaldehyde. The cadmium-109 content was subsequently determined by counting the samples. The cadmium-109 used in these studies was obtained as cadmium chloride ($CdCl_2$) in 0.5M hydrochloric acid (HCl) solution. The specific activity was 2.28 millicuries per gram (mCi/g) Cd and the purity was 90 percent.

All samples were counted using a NaI(Tl) well crystal connected to a single channel analyzer. Samples were counted for up to 40 minutes and sample collection was discontinued when the counting errors exceeded 30 percent. Doses consisted of aliquots taken from either of two cadmium chloride solutions of known dilution. The doses were verified by taking aliquots identical to those used as doses, diluting them volumetrically, and counting measured volumes of these dilutions.

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RESULTS AND DISCUSSION

As shown in Table 1, 3 days following a single oral administration of cadmium-109, as the chloride, to rats having intact bile ducts, about 4 x 10^{-3} percent of the cadmium had been excreted in the urine, while 82 percent was excreted in the feces. Thirteen percent of the dose was recovered in the tissue. After a similar dose to rats with ligated bile ducts, 5 x 10^{-2} per cent was excreted in the urine and about 71 percent in the feces. The tissue retained about 30 percent of the dose.

Rats with intact bile ducts excreted about 5 x 10^{-1} percent of the intravenous cadmium dose in the urine while rats with ligated bile ducts excreted about 2 percent in the urine. About 8 percent of the dose was excreted via the feces of rats with intact bile ducts compared to only about 6 x 10^{-1} percent by bile duct-ligated rats. The percentage of the dose recovered in the tissues was 91 and 96 respectively for the intact and ligated rats. This may indicate that only about 5 percent of the cadmium was excreted via the bile, whereas in a similar study using lead nitrate, as much as 20 percent of the lead was excreted into bile following intravenous administration. In the same time period, following an oral dose with cadmium, about 17 percent was retained in the tissue compared with only 2 percent of a lead dose administered in a similar manner (see Table 3).

The decrease in the amount of cadmium secreted into the bile following intravenous administration as compared to that following its oral administration, is probably due to suppression of biliary excretion by cadmium. Frazier and Kingsley (1976), using an isolated perfused rat liver demonstrated that cadmium concentration in the bile increases with increasing dose until a threshold is reached at about 17 μmol. At this concentration of cadmium chloride, bile formation is significantly reduced. Frazier and Kingsley felt that the reduced bile formation is a manifestation of a direct toxic effect of cadmium on active transport of bile salts or sodium, either by modification of the hepatocyte bile membrane or by decoupling, energy-yielding processes. They indicated that liver respiration also decreases at higher cadmium doses.

Frazier and Kingsley (1976), have also shown a direct relationship between the cadmium uptake by the liver and the amount of zinc lost by the liver at low dose levels. This relationship appears to be due to a cadmium-zinc "exchange" mechanism representing either a direct replacement of zinc by cadmium or by the utilization of the normal zinc resorption pathway by cadmium. At higher cadmium exposures this "exchange" mechanism becomes less important relative to simple diffusion of cadmium which is independent of zinc transport. They also showed that cadmium blocked zinc uptake.

In 1974 Cikrt and Tichy investigated biliary excretion of cadmium in rats following in vivo bile duct cannulation, whereby a threshold for cadmium excretion into the bile was found. At doses below 1 μmol, little cadmium is secreted into the bile and less than 2 percent of the dose is taken up by the liver. Above 1 μmol, 6 to 8 percent of the dose is excreted into the bile. At 17 to 19 μmol, this percentage decreases again due to reduced bile production.

The dose levels administered in our study, although less than the 17 to 19 μmol of cadmium, may be high enough to marginally affect bile production. Cikrt and Tichy (1974) found that 67.3 percent of an injected dose of 1.07 μmol of cadmium was retained in the liver. Of this amount, 7 to 8 percent was excreted in the bile. Using these figures, it appears that about 5 percent of the total dose is excreted in the bile. This figure compares favorably with our results, which indicate that about 5 percent more of the dose was retained in the tissues of the bile-ligated rats than was retained in the tissues of intact rats.

In those tissues selected for comparison with lead concentration (Table 4) cadmium was shown to be more concentrated in all tissues other than bone. The percent of cadmium dose estimated in total bone was less than that of lead following oral administration.

Many researchers have found that the liver is the primary organ of concern in mammalian species during the initial stages of cadmium uptake (Nordberg et al. 1971; Shaikh and Lucis 1972; Webb 1972; Winge and Rajagopalan 1972; Tanaka and Sueda 1973; Colucci et al. 1975; Horner and Smith 1975; Neathery and Miller 1975; Frazier and Kingsley 1976). The data from our studies show the highest concentrations of cadmium were reached in the liver 3 days after the administration of cadmium-109 chloride. Tsuchiya et al. (1972) estimated the biological half-time to be 7 years in the liver of humans.

Long-term retention also occurs in the kidneys and bone. Friberg et al. reported in 1971 that cadmium had a biological half-life in the human kidney of between 16 and 17 years. Bone appears to concentrate cadmium, as it has been implicated in the formation of "itai-itai disease," a form of osteomolacia (Friberg et al. 1974). Ando et al. in 1977 demonstrated that calcium absorption from the gastrointestinal tract and its incorporation into bone was blocked in rats exposed to cadmium chloride. Sakai et al. (1975) found similar results in chick embryo tibia when cadmium was added to tissue culture medium.

Placental transfer of cadmium was not studied, as the literature indicates a limited passage of cadmium across the placental barrier (Friberg et al. 1971; Friberg et al. 1973). A calcium macromolecule, which may be responsible for preventing significant amounts of cadmium from entering the fetus, has been isolated from the rat placenta (Lucis et al. 1972). In addition, a large cadmium-binding protein isolated from the mammary gland of lactating rats may have an important role in limiting cadmium transfer to milk (Lucis et al. 1972).

TABLE 1. AVERAGE PERCENT OF ADMINISTERED CADMIUM DOSE RECOVERED

Method of Administration and Treatment	No. of Rats	Urine Mean Std. Deviation	Feces Mean Std. Deviation	Tissue Mean Std. Deviation
Oral				
Non-ligated	6	$4.25 \pm 2.73 \times 10^{-3}$	81.9 ± 17.4	12.8 ± 5.9
Ligated	6	$5.00 \pm 2.30 \times 10^{-2}$	70.7 ± 14.5	30.1 ± 6.1
I. V.				
Non-ligated	6	$4.92 \pm 2.87 \times 10^{-1}$	7.99 ± 1.44	90.9 ± 23.1
Ligated	6	1.69 ± 1.43	$5.52 \pm 4.31 \times 10^{-1}$	95.9 ± 26.2

TABLE 2. AVERAGE PERCENT OF CADMIUM DOSE RECOVERED PER TISSUE

Tissue	Oral		Intravenous	
	Ligated	Non-Ligated	Ligated	Non-Ligated
Liver	1.86 ± 0.89	1.64 ± 0.67	39.3 ± 14.8	30.1 ± 10.4
Spleen	$4.65 \pm 0.79 \times 10^{-2}$	$4.49 \pm 0.81 \times 10^{-2}$	$4.37 \pm 3.51 \times 10^{-1}$	$4.60 \pm 0.98 \times 10^{-1}$
Kidney	0.21 ± 0.08	$6.88 \pm 3.58 \times 10^{-2}$	7.45 ± 1.95	7.36 ± 4.16
Heart	$3.20 \pm 0.27 \times 10^{-2}$	$3.05 \pm 0.40 \times 10^{-2}$	$2.96 \pm 0.57 \times 10^{-1}$	$2.30 \pm 1.52 \times 10^{-1}$
Brain	$2.20 \pm 0.24 \times 10^{-2}$	$2.01 \pm 0.35 \times 10^{-2}$	$2.85 \pm 0.76 \times 10^{-2}$	$2.19 \pm 1.50 \times 10^{-1}$
Skull	$4.36 \pm 0.93 \times 10^{-2}$	$3.02 \pm 1.01 \times 10^{-2}$	$4.20 \pm 1.13 \times 10^{-1}$	$2.09 \pm 1.72 \times 10^{-1}$
Bone*	$4.23 \pm 0.55 \times 10^{-2}$	$1.90 \pm 0.32 \times 10^{-2}$	2.82 ± 0.22	3.16 ± 0.12

*Estimation based on percentage of body weight assigned to the bone of adult rats as reported by Sikor and Mahlum.

TABLE 3. COMPARISON OF LEAD-210 WITH CADMIUM-109 RECOVERED IN RATS AS A PERCENTAGE OF THE ADMINISTERED DOSE

Method of Administration and Treatment	Urine		Feces		Tissue	
	Cadmium	Lead	Cadmium	Lead	Cadmium	Lead
Oral						
Non-ligated	$4 \pm 3 \times 10^{-3}$	$1 \pm 0.6 \times 10^{-1}$	82 ± 17	95 ± 3	13 ± 6	5 ± 3
Ligated	$5 \pm 2 \times 10^{-2}$	$1 \pm 6 \times 10^{-1}$	71 ± 14	93 ± 3	30 ± 6	7 ± 3
I. V.						
Non-ligated	$5 \pm 3 \times 10^{-1}$	6 ± 6	8 ± 1	24 ± 10	91 ± 23	71 ± 13
Ligated	2 ± 1	4 ± 3	6 ± 4	7 ± 7	96 ± 26	88 ± 9

TABLE 4. COMPARISON OF THE AVERAGE PERCENT OF DOSE RETAINED IN RAT TISSUE 3 DAYS AFTER ADMINISTRATIONS OF A SINGLE ORAL DOSE

Method of Administration and Treatment	Liver		Kidney		Bone	
	Cadmium	Lead	Cadmium	Lead	Cadmium	Lead
Oral						
Non-ligated	2 ± 1*	$3 \pm 3 \times 10^{-2}$	$7 \pm 4 \times 10^{-2}$	$6 \pm 5 \times 10^{-2}$	$2 \pm 3 \times 10^{-2}$	2×10^{-1}
Ligated	2 ± 1	$6 \pm 2 \times 10^{-2}$	$2 \pm 1 \times 10^{-1}$	$4 \pm 1 \times 10^{-2}$	$4 \pm 1 \times 10^{-2}$	1
I. V.						
Non-ligated	30 ± 10	2 ± 2	7 ± 4	1 ± 1	3 ± 0.2	1×10^{-1}
Ligated	39 ± 15	6 ± 7	7 ± 2	3 ± 2	3 ± 0.1	1×10^{-1}

*Mean ± Standard Deviation

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